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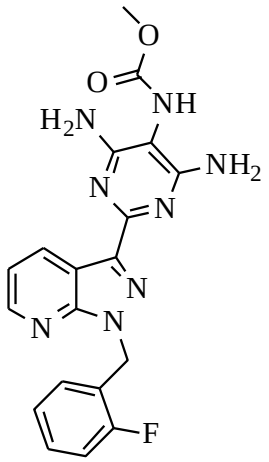
Process For The Preparation Of Methyl (4,6-Diamino-2-(1-(2-Fluorobenzyl)-1H-Pyrazolo[3,4-B]Pyridin-3-Yl)Pyrimidin-5-Yl)Carbamate

MSN Laboratories Private Limited, R&D Center; Srinivasan Thirumalai Rajan; M Venkatesh; Ramakrishna Bommidi; Balakrishna Gunupuru

Process for the preparation of methyl (4,6-diamino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b] pyridin-3-yl) pyrimidin-5-yl)carbamate

The present invention provides process for the preparation of methyl (4,6-diamino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b] pyridin-3-yl)pyrimidin-5-yl)carbamate compound of formula-1, represented by the following structural formula:



Formula-1

Methyl(4,6-diamino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate is a process intermediate for the preparation of Riociguat.

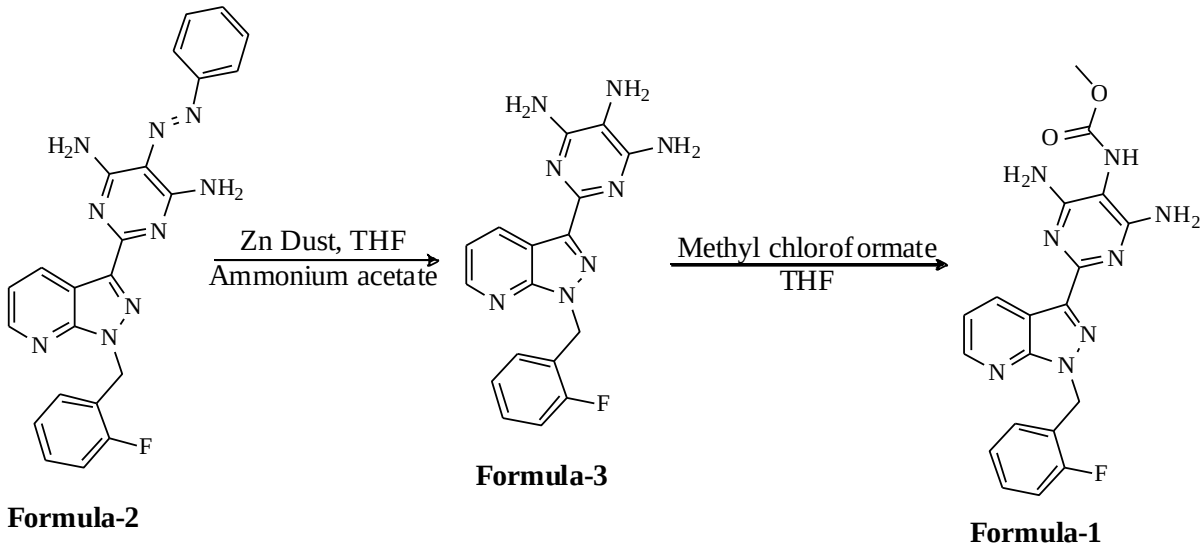
Riociguat is a stimulator of soluble guanylate cyclase (sGC). It was approved by the U.S. Food and Drug Administration in October, 2013. It is used to treat two forms of pulmonary hypertension (PH): chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). Riociguat constitutes the first drug of the class of sGC stimulators.

US Patent No. 7173037 B2 discloses Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate and process for its preparation.

WO 03/095451 describes the preparation of Methyl (4,6-diamino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate compound of formula-1.

The present invention provides improved process for the preparation of Methyl (4,6-diamino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate of compound of formula-1, which provides Riociguat with high yield and purity. Also, the said process is cost effective and commercially viable.

Process of the present invention is schematically represented as below:



Formula-2 **Formula-3** **Formula-1**

Examples:

Example-1: Preparation of methyl (4,6-diamino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate

Methanol [250 ml] and Tetrahydrofuran [250 ml] were added to (E)-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-(phenyldiazenyl)pyrimidine-4,6-diamine [100 g] at 25-30°C. Cooled the mixture to 5-10°C. Ammonium acetate [70.14 g] was added to the mixture at 5-10°C and stirred the mixture for 15 minutes. Zinc dust [36.35 g] was slowly added to the mixture at 5-10°C and stirred the mixture for 2 hours. Mixture filtered using hy-flow bed and bed washed with methanol. Slowly water (1000 ml) was added to the obtained filtrate at 25-30°C and stirred for 60 minutes. Adjusted the mixture pH between 2-3 by using hydrochloric acid at 25-30°C and stirred for 60 minutes. Filtered the solid and washed with water. Water (1000 ml) was added to the obtained solid at 25-30°C and adjusted the mixture pH between 8-9 by using sodium carbonate solution. Stirred the mixture for 60 minutes at 25-30°C. Filtered the solid and washed with water. Dried the compound at 60-65°C for 14 hrs.

Above obtained solid was added to the mixture of tetrahydrofuran (490 ml) and sodium bicarbonate solution (sodium bicarbonate 20.1 g and water 56 ml) at 25-30°C and stirred for 15 minutes. Cooled the mixture to 5-10°C. Slowly methyl chloroformate (22.6 g) was added to the mixture at 5-10°C and stirred for 5 hrs. Slowly water (1260 ml) was added to the mixture at 10-15°C. Raised the mixture temperature to 25-30°C and stirred for 16 hrs. Filtered the

precipitated solid and washed with water. Dichloromethane (1050 ml) and methanol (1050 ml) were added to the obtained wet solid at 25-30°C and stirred for 10 minutes. Under stirring carbon powder (28 g) and silica gel (14 g) were added to the mixture at 25-30°C and stirred for 2 hrs. Mixture filtered through hy-flow bed and bed washed with 1:1 solvent mixture of dichloromethane and methanol. Distilled-out the solvent from filtrate. Dimethylformamide (140 ml) was added to the mixture at 25-30°C. Heated the mixture to 70-75°C. Ethyl acetate (350 ml) was slowly added to the mixture at 70-75°C and stirred for 30 minutes. Cooled the mixture to 25-30°C and stirred for 2 hrs. Filtered the solid and solid washed with ethyl acetate (140 ml). Water (350 ml) was added to the obtained solid at 25-30°C. Heated the mixture to 45-50°C and stirred for 2 hours. Cooled the mixture to 25-30°C and stirred for 2 hrs. Filtered the solid and washed with water. Dried the obtained solid to get titled product.

Yield: 41.5 g; **Purity by HPLC:** 99.33%

Example-2: Preparation of 2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidine-4,5,6-triamine

Methanol [250 ml] and Tetrahydrofuran [250 ml] were added to (E)-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-5-(phenyldiazenyl)pyrimidine-4,6-diamine [100 g] at 25-30°C. Cooled the mixture to 5-10°C. Ammonium acetate [70.14 g] was added to the mixture at 5-10°C and stirred the mixture for 15 minutes. Zinc dust [36.35 g] was slowly added to the mixture at 5-10°C and stirred the mixture for 2 hours. Mixture filtered using hy-flow bed and bed washed with methanol. Slowly water (1000 ml) was added to the obtained filtrate at 25-30°C and stirred for 60 minutes. Adjusted the mixture pH between 2-3 by using hydrochloric acid at 25-30°C and stirred for 60 minutes. Filtered the solid and washed with water. Water (1000 ml) was added to the obtained solid at 25-30°C and adjusted the mixture pH between 8-9 by using sodium carbonate solution. Stirred the mixture for 60 minutes at 25-30°C. Filtered the solid and washed with water. Dried the compound at 60-65°C for 14 hrs. to obtain titled product.

Yield; 71 g

Example-3: Preparation of methyl (4,6-diamino-2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate

2-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidine-4,5,6-triamine (71 g) was added to the mixture of tetrahydrofuran (490 ml) and sodium bicarbonate solution (sodium bicarbonate 20.1 g and water 56 ml) at 25-30°C and stirred for 15 minutes. Cooled the mixture to 5-10°C. Slowly methyl chloroformate (22.6 g) was added to the mixture at 5-10°C

and stirred for 5 hrs. Slowly water (1260 ml) was added to the mixture at 10-15°C. Raised the mixture temperature to 25-30°C and stirred for 16 hrs. Filtered the precipitated solid and washed with water. Dichloromethane (1050 ml) and methanol (1050 ml) were added to the obtained wet solid at 25-30°C and stirred for 10 minutes. Under stirring carbon powder (28 g) and silica gel (14 g) were added to the mixture at 25-30°C and stirred for 2 hrs. Mixture filtered through hy-flow bed and bed washed with 1:1 solvent mixture of dichloromethane and methanol. Distilled-out the solvent from filtrate. Dimethylformamide (140 ml) was added to the mixture at 25-30°C. Heated the mixture to 70-75°C. Ethyl acetate (350 ml) was slowly added to the mixture at 70-75°C and stirred for 30 minutes. Cooled the mixture to 25-30°C and stirred for 2 hrs. Filtered the solid and solid washed with ethyl acetate (140 ml). Water (350 ml) was added to the obtained solid at 25-30°C. Heated the mixture to 45-50°C and stirred for 2 hours. Cooled the mixture to 25-30°C and stirred for 2 hrs. Filtered the solid and washed with water. Dried the obtained solid to get titled product.

Yield: 41.5 g; **Purity by HPLC:** 99.33%

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